

HIGH DOSAGE PROCAINE PENICILLIN COMBINED WITH AMPICILLIN IN THE TREATMENT OF GONORRHOEA AFTER FAILURE WITH STANDARD PROCAINE PENICILLIN DOSAGE*

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This is a preliminary report suggesting a method of management of cases of gonorrhoea in which there has been failure of treatment with standard doses of penicillin.

Over the past 10 years there has been a steady increase in the number of strains of gonococci isolated which show an increased resistance to the action of penicillin (Curtis and Wilkinson, 1958). The Medical Research Council (1961) published a study of cases in Great Britain, which showed that 13.2 per cent. of strains of gonococci isolated before treatment were inhibited only by concentrations of penicillin as high as 0.125 to 1.0 units per ml.

Recent work by Smith and Levey (1967) in Australia, indicates a more alarming picture; they found that 46 of 104 strains isolated in 1966 showed a decreased sensitivity to penicillin *in vitro*. Nine of the strains were resistant at a minimum inhibitory concentration of 0.1 unit per ml., 27 at 0.5 unit per ml., 9 at 1.0 unit per ml., and 1 at 2.5 units per ml.

In an attempt to maintain a high cure rate, the dosage of penicillin routinely employed in the treatment of gonorrhoea has gradually been increased in the last few years, but this trend must inevitably reach a point at which further increase is unreasonable. It is vitally important from the epidemiological viewpoint to prevent the "escape" of strains of gonococci showing increased resistance to the action of penicillin, and for this reason the treatment to be employed in cases of failure of treatment with routine doses of penicillin should be as effective as possible.

Present Investigations

With this in mind the following regime for the treatment of such failures was proposed. There are three different schedules for comparison.

(A) Initially, treatment was given in 51 cases using a single dose of procaine penicillin 3.6 mega units intramuscularly. These 51 cases occurred in fifty patients, one West Indian having two infections; 27 of the patients were born in the United Kingdom, fourteen were from the West Indies, and nine from elsewhere. 36 patients were single and twelve were married; in two cases the marital state was unknown. 27 (54 per cent.) of the patients gave previous histories of similar episodes. 45 of the 51 cases could be followed up, and treatment failure was seen in three instances (6.7 per cent.).

(B) In the other two series of cases, treatment was given with procaine penicillin 3.6 mega units combined with 2 g. ampicillin taken in the form of four capsules of 500 mg. immediately after the injection had been given.

(1) In the first group receiving this treatment there were 28 patients with infections hitherto untreated; 21 had been born in the United Kingdom two each were from the West Indies and South Africa, and one each from Ireland, Gibraltar, and Malaysia. 23 of the patients were single, one was divorced, one was separated, and three were married. Their ages ranged from 19 to 46 years (mean 27.5). Ten (35.7 per cent.) gave a history of previous infection.

Result 24 of the 28 patients treated attended for follow-up and no instances of treatment failure were observed.

(2) In the main series of sixty cases, treatment with the combination of penicillin and ampicillin was given after treatment with standard remedies had failed:

(a) In 49 instances the routine treatment had

*Received for publication August 1, 1968.

taken the form of a single injection of 0.9 mega units of procaine penicillin; in two of these, there had been failure with tetracycline before the failure with penicillin.

- (b) In nine cases the first treatment had been with 1.8 mega units procaine penicillin, in one case with 3.6 mega units, and in one case with kanamycin 2g. intramuscularly.

The patient who had received 3.6 mega units of penicillin developed right orchitis and Tysonitis 3 days later, both of which were cured by the combined penicillin-ampicillin treatment.

Of this series of sixty patients, 36 were born in the United Kingdom, six were West Indians, and there were two each from Australia, U.S.A., Hungary, and Italy, and one each from Pakistan, Cyprus, Syria, Ghana, Turkey, Egypt, Sierra Leone, Spain, South Africa, and Venezuela. Their ages ranged from 8 to 46 years (mean 28.3). 51 were single, 8 were married, and one was separated. In 39 instances the identity of the original source of infection was known, in 19 it was unknown, and two of the patients denied any previous exposure. Four of the patients had acquired their infections from homosexual practices. Twenty patients (33 per cent.) gave past histories of venereal disease.

Result The numbers of cases on each of the days after initial treatment in which the diagnosis of treatment failure was made are shown in Table 1.

TABLE I
CASES IN WHICH FAILURE WAS DIAGNOSED

1st day of Failure	No. of Cases
2	2
3	14
4	10
5	9
6	7
7	6
8	5
9	0
10	1
11	2
12	2
13	1
14	1

In every instance, the grounds for believing that treatment failure and not re-infection had occurred was the presence of continuous slight discharge or of persistent pyuria. After treatment of these sixty cases with procaine penicillin 3.6 mega units intramuscularly together with 2 g. ampicillin orally 54 were followed up and there were three failures (5.5 per cent.).

In two of these cases of failure, the organism was barely sensitive to an *in vitro* concentration of 0.5 unit penicillin per ml.

Discussion

It is emphasized that this is a pilot survey and insufficient to be of statistical significance. Nevertheless, results are promising, although with other forms of infection, such as rectal gonorrhoea, they do not seem to be as satisfactory. It is hoped to produce further evidence in due course.

Blood Levels of Ampicillin and Procaine Penicillin

As well as the clinical assessment of a single dosage of procaine penicillin and ampicillin in the initial treatment of gonorrhoea and also in the re-treatment of cases of treatment failure, penicillin and ampicillin blood levels were estimated by Mr. R. Sutherland of the Department of Bacteriology, Beecham Research Laboratories. The results in 85 patients are shown in Table II.

TABLE II
BLOOD LEVELS OF AMPICILLIN AND PENICILLIN

Dosage	No. of Cases	Time (hrs)	Total Penicillin Activity (µg./ml.)		Total Ampicillin Activity (µg./ml.)	
			Range	Mean	Range	Mean
3.6 m.u. procaine penicillin + 2 g. ampicillin	4	0-1½	2.65 - 9.3	5.55	2.6 - 6.9	4.26
	21	1½-3	3.05 - 31.5	8.3	3.8-31.0	8.2
	3	3-4½	2.7 - 4.2	3.5	2.4- 4.2	3.2
	5	4½-6	2.1 - 4.6	2.97	1.8- 4.2	2.6
	1	6-7½		1.90	< 1.0	
	1	15-16½		1.55	< 1.0	
	1	19½-21		1.0	< 1.0	
	7	22½-24	0.02 - 1.20	0.76	< 1.0	
	9	48	0.041-0.79	0.27	< 1.0	
3.6 m.u. procaine penicillin alone	2	0-1½	4.66 - 5.00	4.83		
	9	1½-3	0.14 - 9.66	3.1		
	2	3-4½	1.00 - 1.12	1.06		
	1	19½-21		0.92		
	16	22½-24	0.016-1.48	0.73		
	1	27		0.41		
	1	48		0.56		
1	72		0.24			

These results indicate that the early total penicillin activity is essentially very similar for the patients treated with the combined administration of procaine penicillin 3.6 mega units plus ampicillin 2 g. and for those treated with procaine penicillin 3.6 mega units alone. This observation becomes even more significant when it is seen that the early total penicillin activity in the group receiving the combined treatment is almost entirely due to the ampicillin, only a small amount being due to penicillin G.

A possible explanation for this observation is that the dosage of ampicillin used in the combined series produced a plateau blood level of penicillin almost

precisely the same as that produced by the procaine penicillin. However, the more rapid absorption of the drug administered by mouth (in this case the ampicillin) "saturates" the blood and abolishes the diffusion gradient from the depot of the preparation given by intramuscular injection (in this case procaine penicillin).

By definition, the Diffusion Constant k of a given substance is the quantity of material that diffuses across a surface 1 sq. cm. in area in a unit time under a unit concentration gradient, hence

$$k = \frac{(Q)}{(ATC/c)}$$

where Q is the quantity of diffusion material that passes across a plane of area A in time T under a concentration gradient C/c .

In a given example Q may be calculated from the product of the blood level and the blood concentration, assuming the intramuscular depot to be spherical in shape. A may be calculated from the volume administered, and the concentration gradient C/c may be read off from the graph of blood levels against time. The value for k of the preparation of penicillin administered can therefore be calculated.

Once the value for the diffusion constant has been determined, it is possible to calculate the quantity of the depot preparation Q that passes into the blood stream in a given time T :

$$Q = k A T C/c$$

And similarly, the time for the total dose to be absorbed:

$$T = \frac{(Q)}{(k A C/c)}$$

this formula gives an S-shaped curve when geometrical increments of dose are plotted against the time taken for the whole of the depot to diffuse into the blood stream.

Thus the increase of dosage of penicillin given by intramuscular injection cannot be expected to give higher plateau blood levels, but the duration of the plateau will be longer with the higher dosage and this factor is likely to be responsible for a greater number of clinical successes with a higher dosage.

The action of the ampicillin administered by mouth concomitantly with an intramuscular injection of procaine penicillin is to produce the pheno-

menon of depot conservation. By this is meant that the diffusion of any material from the depot is inhibited by the fact that the level of penicillin in the blood is already high. When the total penicillin activity in the blood which is due to the ampicillin has subsided, then diffusion can commence from the intramuscular depot, so that the duration of effect is prolonged. This method of prolonging the effect of penicillin has several practical advantages:

(1) The complete treatment can be administered under supervision in the clinic and does not depend upon the patient remembering to take tablets of probenecid at certain set intervals after he has left the clinic; (2) as Willcox (1965) has shown, ampicillin is slightly more effective against the gonococcus than is penicillin G.

The results of the penicillin blood level determination show:

- (1) That the plateau level of penicillin is prolonged when ampicillin is administered with penicillin.
- (2) That the technique of depot inhibition by the administration of an allied drug capable of independent assay appears to be a workable method for determining the time-dose relationships for various types of penicillin administered by injection.
- (3) Since diffusion of penicillin from an intramuscular depot obeys the physico-chemical laws of diffusion, it is suggested that a practical method of achieving a higher blood concentration after the injection of a given dose of penicillin would be to employ a solution having a greater concentration of penicillin per ml.

Summary

A pilot trial of a new method, using large doses of intramuscular procaine penicillin combined with oral ampicillin, in the treatment of patients in whom gonorrhoea had not been cured with standard dosages of penicillin is described. The success rate was 94 per cent. Estimations of blood levels of procaine penicillin and ampicillin and also of procaine penicillin alone are set forth and discussed. It is concluded that this method of treatment appears to be very promising and that further investigations are indicated.

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Hautes doses de pénicilline-procaïne associées avec l'ampicilline après échec dans le traitement de la gonococcie de doses standard de pénicilline-procaïne

RÉSUMÉ

On commente un essai-pilote d'une nouvelle méthode, utilisant de larges doses de pénicilline-procaïne associées

avec l'ampicilline orale, dans le traitement de gonococques qui n'ont pas guéri par les doses usuelles de pénicilline. Le taux de succès fut de 94 pour cent. L'estimation des niveaux sanguins de l'association aussi bien que de la pénicilline-procaïne seule est présentée et discutée. On conclut que cette méthode de traitement semble très prometteuse et que des recherches ultérieures sont indiquées.